Title: Dietary Sugars, Exercise and Hepatic Carbohydrate Metabolism

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Abstract

This paper reviews the physiological responses of human liver carbohydrate metabolism to physical activity and ingestion of dietary sugars. The liver represents a central link in human carbohydrate metabolism and a mechanistic crux point for the effects of dietary sugars on athletic performance and metabolic health. As a corollary, knowledge regarding physiological responses to sugar ingestion has potential application to either improve endurance performance in athletes, or target metabolic diseases in people who are overweight, obese and/or sedentary. For example, exercise increases whole-body glycogen utilisation, and the breakdown of liver glycogen to maintain blood glucose concentrations becomes increasingly important as exercise intensity increases. Accordingly, prolonged exercise at moderate-to-high exercise intensity results in depletion of liver glycogen stores unless carbohydrate is ingested during exercise. The exercise-induced glycogen deficit can increase insulin sensitivity and blood glucose control, and may result in less hepatic lipid synthesis. Therefore, the induction and maintenance of a glycogen deficit with exercise could be a specific target to improve metabolic health and could be achieved by carbohydrate (sugar) restriction before, during and/or after exercise. Conversely, for athletes, maintaining and restoring these glycogen stores is a priority when competing in events requiring repeated exertion with limited recovery. With this in mind, evidence consistently demonstrates that fructose-containing sugars accelerate post-exercise liver glycogen repletion and could reduce recovery time by as much as half that seen with ingestion of glucose (polymers)-only. Therefore, athletes aiming for rapid recovery in multi-stage events should consider ingesting fructose-containing sugars to accelerate recovery.

Introduction

The French physiologist Claude Bernard (1813-1878) is not only one of the first to propose blind experiments to reduce bias[1] but also is credited with the discovery of glycogen in the liver, thus revealing the central role of this organ in the homeostatic regulation of blood glucose concentrations (or "*milieu intérieur"*)[2; 3]. Bernard originally intended to study the metabolism of all types of foods, choosing to start with the putatively *simple* metabolism of sugars. The complexities of sugar metabolism led Bernard to focus on this area for more than 30 years and, in understated fashion, he described this systematic and meticulous undertaking as "research which has not been wholly sterile"[4]. During this time, he found that the portal vein of dogs (the major blood supply to the liver) has little to no glucose, whereas the hepatic vein leaving the liver carries substantial quantities of glucose. This led Bernard to conclude that the liver is a potential source of sugar. This capacity of the liver to supply glucose to the systemic circulation is important when dietary carbohydrate intake is insufficient to meet the carbohydrate demands of tissues such as the brain and muscles. Therefore, during fasting, exercise or consumption of low-carbohydrate diets, the liver can supply glucose for peripheral tissues. Glucose produced by the liver is derived from two sources: the breakdown of stored glycogen (i.e. glycogenolysis), and the *de novo* production of new glucose from precursors such as lactate, glycerol, pyruvate, glucogenic amino acids, fructose and galactose (i.e. gluconeogenesis)[5]. The liver is the largest glycogen store in humans that can be hydrolysed and release glucose into the circulation to sustain blood glucose concentrations, and is also the tissue with the greatest capacity for gluconeogenesis. Therefore, the ability for the liver to supply glucose from both glycogenolysis and gluconeogenesis has important consequences for maintaining metabolic control during exercise, and especially when dietary carbohydrate intake is restricted.

The liver also plays a central role in the postprandial metabolism of carbohydrates. Following intestinal absorption, the liver is one of the first tissues exposed to ingested carbohydrate. Whilst the intestine (and kidneys) can also metabolise some dietary sugar[6] and undertake gluconeogenesis[7], these are quantitatively less important than hepatic metabolism, at least in humans[8]. Various types of sugars are distinctly metabolised by the liver, with potential implications for human health and performance[9; 10]. Accordingly, the aim of this narrative review is to describe the hepatic metabolism of dietary sugars at rest and during exercise, while considering potential implications for human health and (endurance) exercise performance.

Dietary Sugars

Common sugars in the human diet include the monosaccharides: glucose, fructose and galactose; and the disaccharides: sucrose (fructose-glucose), lactose (galactose-glucose) and maltose (glucose-glucose)[9]. Dietary sugars can be consumed from a variety of food sources, which can influence

resultant health effects. The World Health Organization (WHO) classifies sugars into those which are "intrinsic" (e.g. incorporated within the structure of intact fruit and vegetables or lactose/galactose from milk) *versus* "free sugars"[11]. Free sugars are defined by WHO as monosaccharides and disaccharides added to foods and beverages by the manufacturer, cook or consumer, along with sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates. This classification system is useful for distinguishing between food sources of sugar that are energy dense (i.e. free sugars) and thus may contribute to weight gain[11; 12]. However, this classification system does not specifically distinguish between ingestion of glucose-containing sugars and fructose- or galactose-containing sugars in relation to health, nor does it consider the physical activity status of the individual. This is interesting considering the fundamental differences in the intestinal absorption and hepatic metabolism of glucose, fructose and galactose, and how this metabolism is altered during exercise[8; 9; 10].

Before describing the hepatic metabolism of carbohydrates and sugars, it is important to clarify two points. First, the hydrolysis of glucose polymers such as maltodextrin and starch are typically not rate limiting to intestinal absorption[13], and therefore (at least with regards to hepatic metabolism) free glucose, maltose, maltodextrin and starch can all be considered physiologically similar stimuli. Second, in typical human diets, free glucose is rarely consumed alone, but rather is usually consumed alongside fructose or lactose, or is consumed in polymer (non-sugar) form, such as maltodextrin and starch. Accordingly, whilst this review will refer to the specific types of sugars utilised in studies (e.g. glucose only vs fructose-glucose mixtures), it can be viewed that a non-fructose or non-galactose condition (such as glucose or maltodextrin ingestion) is physiologically representative of non-sugar intake (i.e. maltodextrin, starch etc.), whereas fructose-glucose and galactose-glucose co-ingestion represent the physiological responses to typical sugar intake.

Hepatic Metabolism of Sugars at Rest

Glucose and galactose are primarily absorbed across the intestinal lumen via the transport protein sodium-dependent glucose transporter 2 (SGLT2)[14], whereas fructose is primarily absorbed via glucose transporter 5 (GLUT5)[14]. Once absorbed, these sugars are then metabolised very differently. Glucose is preferentially metabolised by extra-splanchnic tissues such as skeletal muscle, the brain and cardiac muscle[15; 16], whilst fructose and galactose are primarily metabolised by the liver and to a lesser extent small bowel enterocytes and proximal renal tubules[10; 17]. Peripheral tissues such as muscle are therefore only exposed to relatively small amounts of fructose and galactose[18; 19].

Compared to galactose, the metabolic fate of fructose is relatively well characterised. At rest, the liver rapidly takes up and metabolises fructose into fructose-1-phosphate (P) via fructokinase (K_m for fructose: ~0.5 mM and V_{max} estimated at ~3 mmol·min^{-1}·g human liver^{-1})[20; 21; 22]. Fructose-1-P is then metabolised into triose-P (3 carbon substrates) via aldolase B[23]. At rest, the majority of fructose-derived triose-P is converted via gluconeogenesis into glucose (~50%) and glycogen (~15-25%), but some of triose-P can be metabolised into pyruvate, then either oxidised within the liver or converted into lactate (~25%), which enters the systemic circulation and can increase blood lactate concentrations[10; 24]. One other fate of ingested fructose is the conversion into fatty acids via the process known as *de novo* lipogenesis[25]. It has been suggested that lactate is the primary precursor to hepatic *de novo* lipogenesis with fructose intake[26], but the proportion of fructose that is ultimately converted into lipid is estimated at <1% and therefore represents a quantitatively minor pathway of disposal[19]. Nevertheless, the effects of ingested fructose on *de novo* lipogenesis may still be important for metabolic health[27].

Quantitative estimates of the metabolic fate of galactose in humans are scarce. It has been suggested that the primary pathway for human galactose metabolism is the Leloir pathway, the enzymes of which show highest activity in the liver[17]. This pathway involves four main steps: 1) phosphorylation of galactose by galactokinase (K_m for galactose: ~0.9 mM and V_{max} estimated at ~1.4 mmol·min^{-1}·g human liver $^{-1}$ [28; 29]) to yield galactose-1-phosphate; 2) conversion of galactose-1-phosphate and uridine diphosphate (UDP) glucose to UDP galactose and glucose-1-phosphate by galactose-1-phosphate uridyltransferase; 3) conversion of UDP-galactose to UDP-glucose by UDP-galactose-4-epimerase; and 4) conversion of UDP-glucose and diphosphate (PPi) to glucose-1-phosphate and uridine triphosphate (UTP) by UDP glucose pyrophosphorylase[17]. Of note, is an alternative pathway for step 2, known as the Isselbacher pathway, whereby galactose-1-phosphate and UTP are converted to UDP-galactose and PPi by the enzymes UDP-galactose pyrophosphorylase and UDP-glucose pyrophosphorylase[17]. Some tracer studies have attempted to determine the metabolic fate of oral galactose in humans, estimating that during ingestion of galactose at a rate of

33 μmol·kg^{-1}·min^{-1} (~135 g over 360 min), the splanchnic uptake of galactose is saturable at ~15 μmol·kg^{-1}·min^{-1}[30; 31]. At this rate of ingestion, it is estimated that ~30-60% of the ingested galactose is converted into glucose[30], mostly via the direct conversation of hexose to glucose (~67%), with some converted via the indirect (hexose to 3 carbon substrates to glucose) pathway (~33%)[31]. Ultimately, the metabolic fate of ingested galactose in humans therefore remains incompletely understood, although it has been speculated that liver glycogen synthesis is a major route[32; 33] (**Figure 1**).

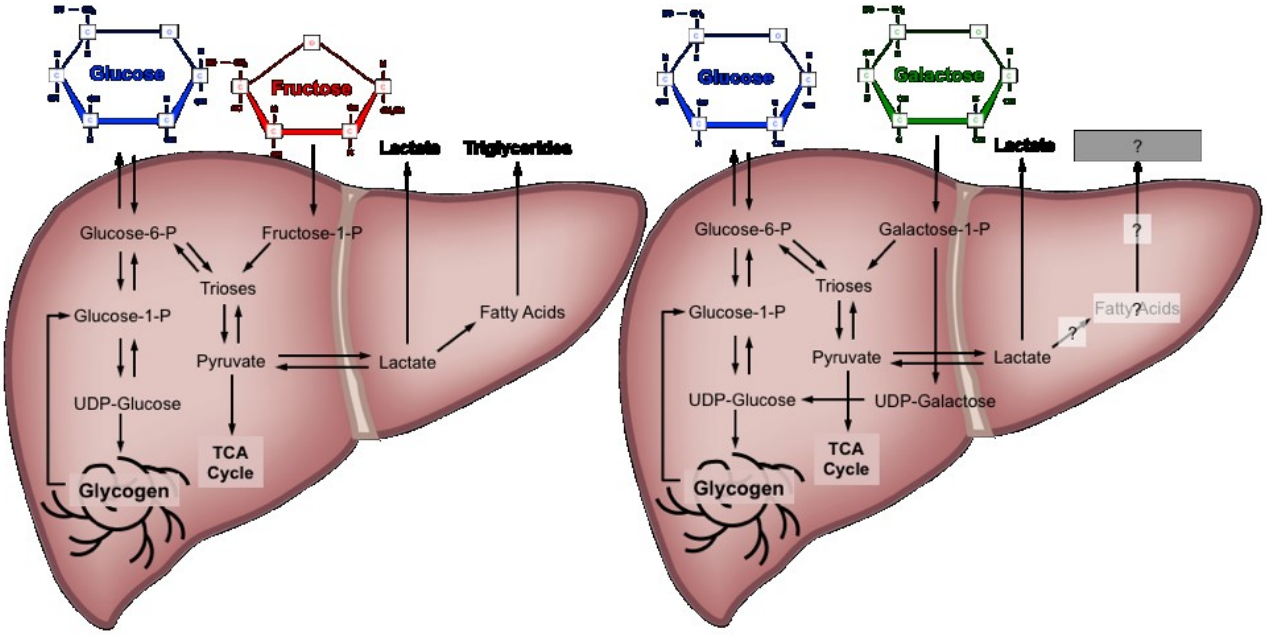

Figure 1. Major metabolic pathways of glucose, fructose and galactose in the human liver. TCA, tricarboxylic acid cycle. Based on references: 10, 17, 23, 24, 25, 26, 30, 31, 32, 33.

Hepatic Metabolism of Carbohydrates with Exercise

Exercise increases energy expenditure, which is predominantly met during prolonged (>30 min) exercise by increases in both carbohydrate and fat oxidation compared to the resting state[34]. The relative contributions of carbohydrate versus fat to exercise metabolism are influenced by the intensity and mode of exercise[35], preceding nutritional status[36; 37; 38], endurance training status[39] and biological sex[40]. Specifically, higher carbohydrate oxidation rates are seen with cycling versus running[35], higher versus lower exercise intensity[34], prior carbohydrate feeding versus fasting[37], in individuals who are less versus more endurance-trained[39] and amongst men *versus* women[40]. Of these predictive factors, the intensity of exercise seems to be the most potent in determining carbohydrate and fat utilisation[34; 41]. Even in highly-trained athletes studied in the overnight fasted state, carbohydrates are the predominant fuel source during moderate-to-high intensity (>50% $\dot{V}O_2$peak) exercise[34]. Exercise is therefore a potent modulator of carbohydrate metabolism, with implications for the fate of ingested carbohydrate.

153 The primary sources of carbohydrate supporting exercise metabolism are muscle glycogen,
154 and circulating glucose and lactate[34]. In the fasted state, almost all the circulating glucose is derived
155 from hepatic glycogenolysis and gluconeogenesis, with minor contributions from the kidneys and
156 intestine[5]. When compared to the capacity to store fat, the relatively limited capacity for humans to
157 store carbohydrate has implications for the ability to sustain moderate-to-high intensity exercise[5].
158 Even amongst lean individuals (~10% body fat), sufficient energy is stored as fat in adipose tissue to
159 theoretically sustain moderate-to-high intensity exercise for many weeks. However, utilising fat as a
160 fuel has a number of limitations in the context of exercise performance. Fat is a relatively "slow"
161 fuel; the rate of adenosine triphosphate (ATP) resynthesis with fat is at least half that when utilising
162 muscle glycogen[42; 43]. Fat is also an "inefficient" fuel on an oxygen basis, requiring ~10% more
163 oxygen consumption for an equivalent energy yield as glucose[44]. Consequently, during high-
164 intensity exercise where rapid ATP resynthesis is required and/or muscle oxygen availability could
165 be limiting, there are advantages to oxidising carbohydrates over fats. Finally, recent evidence implies
166 that glycogen is more than just a fuel and is an important signalling molecule[45]. Low glycogen
167 concentrations in the intramyofibrillar region are associated with impaired sarcoplasmic reticulum
168 calcium release rates and excitation contraction coupling[46]. Therefore, specific depots of glycogen
169 appear to play important roles in both fuelling and regulating skeletal muscle contractile function,
170 hence achieving high carbohydrate availability before and during competition is a goal for athletes
171 competing in almost all endurance sports[47; 48].
172 Low carbohydrate (glycogen) availability in muscle and liver is strongly associated with
173 fatigue during prolonged exercise[49; 50]. The amount of glycogen stored in muscle and liver glycogen
174 prior to single, or repeated bouts of exercise positively correlate with subsequent exercise capacity[49;
175 50]. A number of carbohydrate-related adaptations occur in response to regular endurance training that
176 facilitate improvements in exercise performance. Endurance-trained athletes have a greater capacity
177 to store muscle glycogen, and therefore display an increase in overnight-fasted muscle glycogen
178 concentrations compared to people who are less endurance trained[5; 51]. This increase in basal muscle
179 glycogen concentrations with endurance training is also exaggerated on a high-carbohydrate diet[51],
180 suggesting that endurance-trained athletes can better tolerate high-carbohydrate diets by
181 appropriately storing the excess carbohydrate as muscle glycogen. Interestingly, it seems that basal
182 liver glycogen content does not adapt with endurance training, as endurance-trained athletes tend to
183 exhibit similar liver glycogen concentrations to non-trained controls, when measured in the overnight
184 fasted state[5]. Whether this is also the case in the postprandial state remains to be established.
185 The increase in fasting muscle (but not liver) glycogen concentrations with endurance training
186 provides trained athletes with a larger depot of glycogen to utilise during exercise and so postpones
187 the point at which critically low muscle glycogen concentrations initiate fatigue. In addition to the

greater storage capacity, trained athletes also utilise their muscle glycogen more conservatively during exercise[51]. This sparing of glycogen with endurance training is not specific to muscle, as the rate of liver glycogen utilisation is also attenuated in endurance-trained athletes compared to controls, particularly at moderate-to-high exercise intensities[5]. Evidence regarding whether gluconeogenesis is altered with endurance training is currently equivocal, as some studies indicate endurance training is associated with an increase in absolute rates of hepatic gluconeogenesis[52], whereas others have shown reductions in hepatic gluconeogenesis after endurance training[52]. When pooling all the currently published studies that have concomitantly estimated hepatic glycogenolysis and gluconeogenesis [52; 53; 54; 55; 56; 57; 58; 59; 60; 61; 62; 63; 64; 65; 66], it is clear that endurance training is associated with lower rates of glycogenoloysis (**Figure 2A**), whereas any difference in gluconeogenesis with training status and/or exercise intensity is relatively small and unlikely to be quantitatively important (**Figure 2B**). Furthermore, it is apparent that hepatic glycogenolysis is the predominant source of blood glucose during exercise in an overnight fasted state, and the increase in endogenous glucose appearance with increasing exercise intensity is almost entirely met by an increase in hepatic glycogenolysis, rather than gluconeogenesis (**Figure 2**).

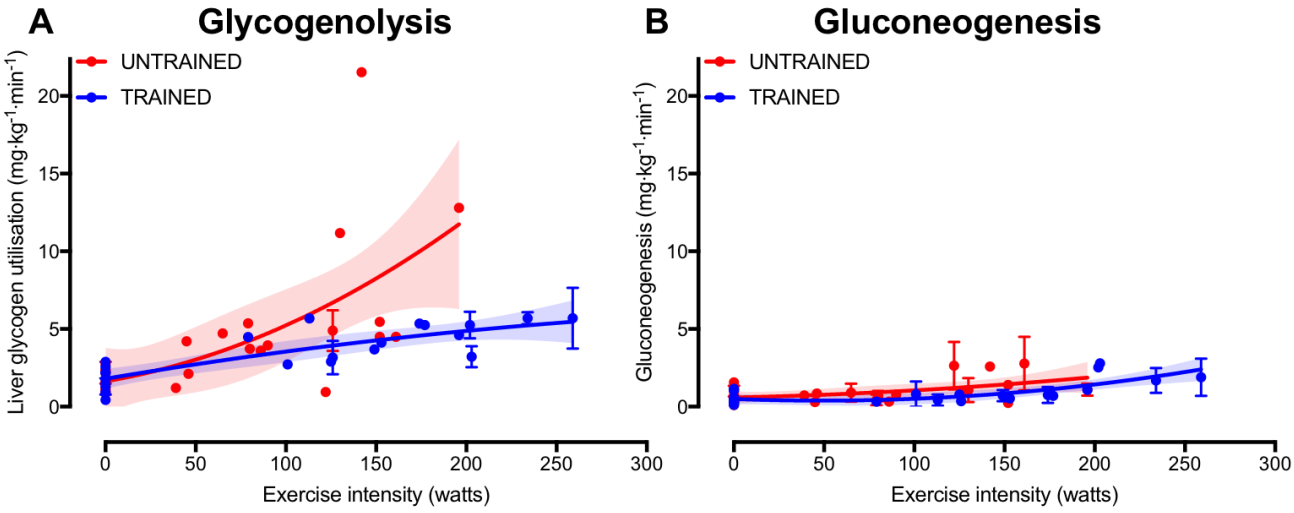

Figure 2. Hepatic glycogenolysis (**A**) and gluconeogenesis (**B**) in endurance trained individuals and untrained individuals. Each dot represents a group of participants or exercise intensity from a study, and error bars represent 95% confidence intervals (only calculated when published data were available to permit this). The shaded areas represent the 95% confidence intervals of the trend lines. Data are from references: 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66.

Interactions between carbohydrate ingestion and exercise occur on multiple levels and in both directions. Ingesting carbohydrates during exercise can increase total carbohydrate oxidation and suppress net liver glycogen utilisation and fat oxidation[67]. Whereas even modest exercise potently re-directs the metabolic fate of orally ingested sugars. For example, 60 minutes of cycling at 100 watts performed 90 min after fructose ingestion diverts more fructose away from storage (e.g. as glycogen) and increases fructose oxidation, without altering the conversion of fructose to glucose[68].

This may partly explain why daily exercise can completely prevent the increase in plasma triglyceride concentrations seen with high fructose intakes[69]. Remarkably, the protection offered from exercise against fructose-induced hypertriglyceridemia is seen independently from changes in net energy balance[69], yet current recommendations for the health effects of dietary sugars rarely consider the context of physical activity status.

Since low carbohydrate availability is associated with impaired exercise tolerance, athletes engaging in competitive endurance events regularly consume carbohydrates during exercise[70]. When ingesting glucose alone, the maximal rate at which humans can digest, absorb and metabolise glucose is ~1 g·min^{-1}[9], which typically only represents ~44% of total carbohydrate oxidation during exercise at moderate intensity (~60% $\dot{V}O_2$peak) and is therefore insufficient to fully meet the carbohydrate requirements of cycling-based exercise[71]. Consequently, oral ingestion of glucose is unable to prevent muscle glycogen depletion during prolonged exercise[67]. It is thought that the primary limitation to the metabolism of orally ingested glucose lies in the splanchnic region, and intestinal absorption of glucose appears to be saturated at ~1 g·min^{-1}[9]. Ingesting glucose at rates higher than 1 g·min^{-1} during exercise is therefore likely to lead to accumulation of glucose in the gut and cause gastrointestinal distress. Interestingly, combining fructose with glucose appears to accelerate the digestion, absorption and utilisation of carbohydrate, such that exogenous carbohydrate oxidation rates can reach up to ~1.7 g·min^{-1}, equating to ~70% of total carbohydrate oxidation[9; 71]. Under these conditions, the relative contribution from endogenous carbohydrate sources is therefore reduced from 100% in the fasted state, to ~30% with very high (2.5 g·min^{-1}) carbohydrate ingestion rates[71]. The primary mechanism by which fructose-glucose mixtures can increase exogenous carbohydrate oxidation over glucose alone is thought to be that intestinal fructose transport utilises a separate pathway than glucose. Specifically, whilst glucose absorption via SGLT-1 is saturated at ~1 g·min^{-1}, fructose is primarily transported via GLUT5, thereby taking advantage of this alternative pathway and delivering more total carbohydrate to the system[9].

Potential Implications and Applications

Exercise Performance

The health and performance implications of carbohydrate intake can be dependent on the specific pathways through which different dietary sugars are absorbed and metabolised. In terms of endurance performance, the accelerated digestion, absorption and utilisation of fructose-glucose mixtures above glucose only, has potential benefits with regards to sparing glycogen stores whilst minimising gastrointestinal distress during exercise[9]. Gastrointestinal complaints are relatively common in endurance events[72], which may directly impair performance, but also limit the ability to ingest adequate nutrition to fuel the demands of the exercise. It has recently been demonstrated that the

ingestion of either glucose alone, or sucrose (glucose-fructose) can prevent liver glycogen depletion during prolonged (3 h) cycling at a moderate exercise intensity (55% VO_2max)[67]. Whilst there was no further benefit of ingesting sucrose compared to glucose with respect to net liver glycogen depletion, the prevention of liver glycogen depletion with sucrose ingestion was attained with lower ratings of both gut discomfort and perceived exertion, compared to glucose ingestion[67]. Furthermore, when carbohydrates are ingested in large amounts during exercise (>1.4 $g \cdot min^{-1}$), the ingestion of glucose-fructose enhances endurance performance by ~1-9% more than when glucose is ingested alone[73]. On the other hand, galactose appears to display relatively low rates of exogenous carbohydrate oxidation during exercise (~0.4 $g \cdot min^{-1}$ oxidised, when ingesting ~1.2 $g \cdot min^{-1}$), despite an apparent potential for faster intestinal absorption of galactose compared to glucose in perfusion studies[74; 75]. Moreover, since galactose primarily shares a common intestinal absorption pathway to glucose, combining galactose and glucose ingestion is unlikely to provide the same benefits for exogenous carbohydrate availability and endurance performance as glucose-fructose co-ingestion.

In addition to manipulating carbohydrate availability *during* exercise, dietary sugars can also play an important role during post-exercise *recovery*, particularly in multi-stage events such as the Tour de France and the Marathon des Sables, where athletes are required to perform to the best of their ability with less than 24 h of recovery. Under these scenarios, the primary limiting factor to recovery time is glycogen storage rate[48; 76]. Even with high carbohydrate intakes, it is thought to take between 20-24 h to fully restore muscle glycogen concentrations after exhaustive exercise[77]. Thus, on moderate carbohydrate diet, muscle glycogen repletion can take up to 46 h[78]. Therefore, intensive nutritional strategies can be applied to optimise muscle glycogen resynthesis post-exercise. Post-exercise muscle glycogen resynthesis rates display a biphasic response, with the most rapid net synthesis seen within the first 30 min following exercise in an insulin-independent phase[79]. Following this period, muscle glycogen synthesis rates become insulin-dependent and can fall to at least half the rate of that seen within the first 30 min post-exercise[79]. Muscle glycogen resynthesis rates are maximally stimulated with carbohydrate ingestion rates of ≥1 $g \cdot kg\ body\ mass^{-1} \cdot h^{-1}$[48; 76], and this ingestion rate is also associated with optimal restoration of endurance capacity during short-term (4-h) recovery periods[76]. Therefore, athletes are advised to consume carbohydrate at a rate of 1-1.2 $g\ carbohydrate \cdot kg\ body\ mass^{-1} \cdot h^{-1}$ during the early stages (4 h) of recovery[47; 48] and, when these ingestion rates are not achievable, the addition of certain (insulinotropic) proteins, such as milk proteins, to carbohydrate can potentially increase the efficiency of muscle glycogen resynthesis[80].

Current sports nutrition guidelines for recovery do not specify whether the carbohydrate should be from a particular source of sugar (e.g. glucose versus fructose versus galactose)[47; 48], which is understandable given that muscle glycogen resynthesis rates do not appear to differ whether glucose or glucose-fructose mixtures are ingested[9; 81], yet overlooks the clear potential for sugars to

differentially affect liver glycogen resynthesis. Indeed, when pooling all currently published data that compare glucose with glucose-fructose mixtures in crossover designs[50; 81; 82; 83; 84; 85], it is apparent that post-exercise muscle glycogen resynthesis rates do not differ between glucose ingested alone versus glucose-fructose (sucrose) mixtures (**Figure 3A**). Extrapolating these data would suggest that 22 h are required to completely re-synthesise muscle glycogen from a fully depleted state, when following current sports nutrition guidelines, regardless of the type of carbohydrate ingested (**Figure 3A**). This indicates that intestinal absorption of carbohydrate is not rate-limiting to post-exercise muscle glycogen resynthesis. On the other hand, liver glycogen resynthesis appears to be potently accelerated by glucose-fructose co-ingestion compared to glucose (polymers) alone (**Figure 3B**)[50; 81; 86], which may be in part due to greater exogenous carbohydrate availability and/or the specific hepatic metabolism of fructose.

A further interesting observation is that liver glycogen resynthesis rates also appear to show a bi-phasic, time-dependent response, albeit in the opposite direction to skeletal muscle. Within the first 2 hours post-exercise, net liver glycogen resynthesis rates are ~30-50% slower than the 3-5 hour period, independent of the type of carbohydrate ingested (2 ± 2 and 5 ± 2 $g \cdot h^{-1}$ in the 0-2 h post-exercise *versus* 4 ± 2 and 8 ± 2 $g \cdot h^{-1}$ in the 2-5 h post-exercise, with glucose and sucrose ingestion, respectively)[81]. Furthermore, with high rates of carbohydrate ingestion, fructose-glucose mixtures can reduce ratings of gut discomfort during recovery from exercise, compared to glucose ingestion alone[81]. Extrapolating these data (i.e. assuming that the first 6.5 h is representative of a full 24-h period) indicates that when only glucose is ingested, complete recovery of liver glycogen stores may take ~25 h (**Figure 3B**). However, when glucose-fructose mixtures are ingested, then liver glycogen repletion could take as little at 11 h (**Figure 3B**). When considering that the time between ending a stage and beginning the next stage in the Tour de France can be ~15 hours, the accelerated recovery of liver glycogen stores with fructose-glucose mixtures is highly meaningful from a practical standpoint.

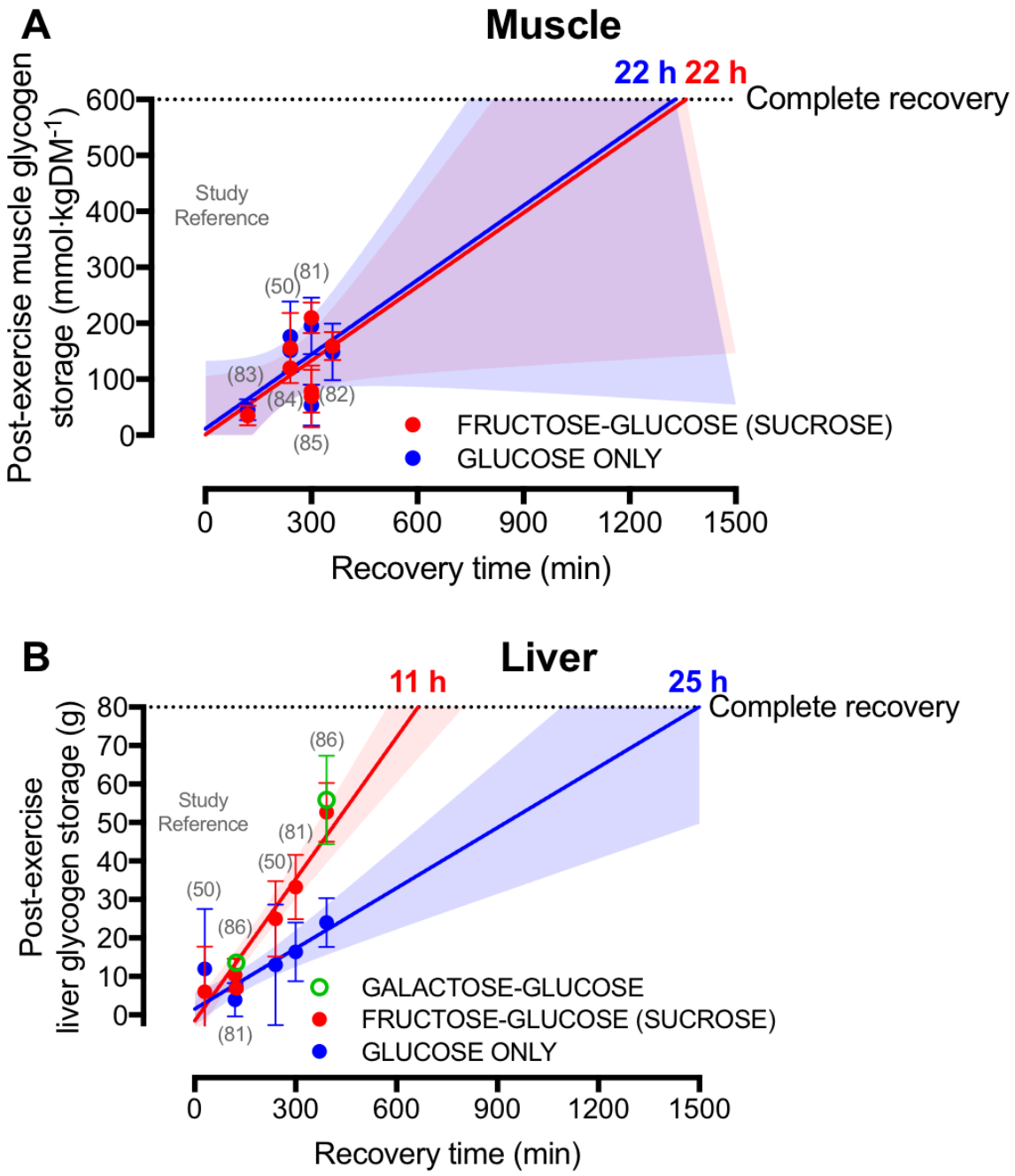

Figure 3. Studies that have directly compared glucose ingestion alone, with either fructose-glucose or galactose-glucose mixtures, and measure rates of muscle (**A**) and liver (**B**) glycogen repletion post-exercise. Each circle represents a timepoint within a study. Error bars represent 95% confidence intervals, and the shaded areas represent the 95% confidence interval of the trend line. For complete recovery of muscle glycogen stores, 600 mmol·kgDM^{-1} was chosen on the basis that muscle glycogen concentrations at exhaustion is typically ~115 mmol·kgDM^{-1} and the maximal muscle glycogen concentrations of relatively well-trained athletes (60-70 mL·kg^{-1}·min^{-1}) is between 600-800 mmol·kgDM^{-1}[(51)]. For complete recovery of liver glycogen stores, 80 g was chosen on the basis that liver glycogen concentrations in the overnight fasted state are ~280 mmol·L^{-1}. Assuming a liver volume of 1.8 L and the molar mass of a glycosyl unit being 162 g/M, this equates to 80 g glycogen[(5)].

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Interestingly, fructose is not the only sugar that more rapidly replenishes liver glycogen contents following exercise than glucose alone. The addition of galactose to glucose also accelerates post-exercise liver glycogen repletion when matched for total carbohydrate intake[86], and to a similar extent as fructose-glucose ingestion (**Figure 3B**). Since intestinal galactose-glucose absorption should theoretically be slower than fructose-glucose absorption, it is tempting to speculate that the mechanisms by which fructose and galactose enhance liver glycogen resynthesis relate to hepatic metabolism, rather than intestinal absorption. These data also raise the following question: if the Leloir pathway (direct galactose-glucose conversion) is the primary pathway of human galactose metabolism, why is the liver glycogenic response to galactose ingestion more comparable to fructose than to glucose? With regards to generating useful data for applied practice, there is a need to establish the optimal dose and mixture of sugars for rapid liver glycogen resynthesis and whether this translates into improved endurance performance. Accordingly, dose-response studies and direct comparisons of combined galactose-fructose-glucose are warranted.

Whilst the effects of fructose-glucose and galactose-glucose ingestion on glycogen resynthesis are interesting and likely to be important for athletic performance, this will remain speculative in the absence of empirical data. Fortunately, a recent study compared the recovery of exercise capacity with glucose-maltodextrin ingestion versus fructose-maltodextrin ingestion[87]. Since the maltodextrin is hydrolysed, absorbed and oxidised as quickly as free glucose[9], it can be considered the glucose-maltodextrin is physiologically almost identical to ingesting pure glucose. Athletes were first asked to run on a treadmill at 70% $\dot{V}O_2$max to exhaustion. Following this, the athletes ingested 90 g carbohydrate per hour during a 4-hour recovery period as either a glucose-maltodextrin mixture, or fructose-maltodextrin mixture. After the recovery period, the athletes ran on the treadmill again at 70% $\dot{V}O_2$max to exhaustion. During the glucose-maltrodextrin trial, the second-bout capacity for these athletes to run was 61.4 ± 9.6 minutes, whereas, when fructose-maltrodextrin was ingested in the recovery period, these athletes ran for 81.4 ± 22.3 minutes representing an improvement in second-bout endurance capacity of ~30%[87]. This provides the first evidence that fructose-glucose ingestion accelerates recovery of exercise capacity. When considered in light of the consistently reported acceleration of liver glycogen recovery, it may be sensible for athletes requiring rapid recovery during multi-stage events to consume fructose-glucose mixtures rather than glucose only. In terms of applying this in practice, it could mean the use of fruit smoothies to supplement carbohydrate intake rather than the commonly held view that pasta is a preferable choice for carbohydrate loading.

Metabolic Health

The impact of dietary sugars on hepatic metabolism also has potential metabolic health consequences. Public health recommendations to limit intake of free sugars are primarily based on the effects of diets high in free sugars on body weight and associations with dental caries[11]. However, distinct metabolic effects of fructose in particular receive much interest with respect to metabolic health. Metabolic health is typically characterised by the ability to maintain relatively stable blood glucose and lipid concentrations in the postprandial state[88], since high postprandial glucose and/or triglycerides concentrations are associated with cardiovascular disease[89; 90]. The ability to maintain relatively stable circulating metabolite concentrations with relatively little need for insulin represents an important aspect of insulin sensitivity, which is thought to be a fundamental mechanism by which metabolic health is sustained. Whilst insulin sensitivity is most commonly associated with blood glucose control, the many regulatory roles of insulin mean that insulin sensitivity is best considered with respect to the tissue of interest and function of interest. For example, insulin sensitivity of skeletal muscle to glucose uptake, insulin sensitivity of the liver to glucose output, or insulin sensitivity of adipose tissue to lipolysis, etc. This is relevant when discussing the role of fructose in metabolic health as it is apparent that most of the metabolic effects of fructose occur in a tissue-specific manner.

The addition of fructose to other ingested nutrients can impact both postprandial glucose and lipid metabolism. Low doses of fructose can in fact lower postprandial glycaemia via increased hepatic glucose disposal secondary to fructose-1-phosphate antagonisation of glucokinase regulatory protein, and thereby enhanced hepatic glucokinase activity[91; 92; 93]. However, compared to glucose ingestion, fructose can enhance postprandial triglyceride concentrations acutely[19] and supplementation of fructose over days/weeks can increase fasting plasma glucose, insulin and triglyceride concentrations, and increase liver fat content, particularly in overweight/obese populations and during positive energy balance[94; 95]. However, some have shown that a positive energy balance and/or saturated fat intake are more potent drivers of liver fat accumulation than specific effects of fructose over glucose[96; 97]. The mechanisms underlying these metabolic changes with fructose ingestion, are thought to include a suppression of hepatic insulin sensitivity to glucose output, stimulation of *de novo* lipogenesis via activation of pyruvate dehydrogenase (upregulated when glycogen concentrations are high[98]), and a reduction in hepatic fatty acid oxidation, leading to increased net lipid synthesis and VLDL-triglyceride production and secretion[10; 69; 95; 99]. This is consistent with data pertaining to post-exercise glycogen resynthesis, since it is thought that insulin resistance to skeletal muscle glucose uptake (leading to hyperglycaemia) and *de novo* lipogenesis (leading to hypertriglyceridemia) are upregulated when glycogen stores are saturated[63; 100; 101]. Furthermore, during non-exercise conditions, the increase in postprandial liver glycogen concentrations seen with a 7-day high-glycaemic index diet occurs in tandem with increases in liver

fat content[102]. The proposed relationship between liver glycogen and lipid metabolism supports the idea that regular exercise can obliterate the negative effects of fructose overfeeding in healthy men[8; 69], since exercise results in rapid glycogen turnover, and there is clear evidence that the carbohydrate deficit from exercise is a key factor in exercise-induced increases in whole-body glucose control[103].

Whether exercise can be protective against fructose-induced hypertriglyceridaemia and changes in hepatic insulin sensitivity in overweight and obese populations remains to be established. Given the role of glycogen status in metabolic health, it could be speculated that, when metabolic control is the primary aim, the avoidance of carbohydrates (and in particular fructose-containing sugars) for periods before, during, and/or after exercise could better maintain some of the insulin-sensitising effects of exercise via greater liver glycogen depletion and delayed liver glycogen repletion (**Figure 3**), but this has never been empirically assessed. Fructose can therefore induce changes that are associated with impaired metabolic health, but this appears to be primarily in sedentary, overweight and obese individuals, and when in a positive energy balance. There is evidence that regular exercise has the potential to protect against most (if not all) of these metabolic effects, at least in healthy men. Research is required to determine whether exercise can be protective against metabolic changes with fructose supplementation in people at risk of metabolic disease, and if so, then to characterise the lowest "dose" of exercise that is protective.

Summary and Conclusions

The liver is a primary site of carbohydrate metabolism and particularly the metabolism of fructose and galactose-containing sugars. Hepatic metabolism plays a key role in metabolic health and endurance exercise performance, by assisting in the maintenance of blood glucose and lipid homeostasis during rapid changes in the supply and demand for energy, such as with fasting-feeding cycles and with physical activity. In the fasted state, the liver provides almost all the glucose necessary to maintain blood glucose concentrations during exercise. As exercise intensity increases, thereby accelerating the demand for glucose by skeletal muscle, the increase in liver glucose output is primarily met by releasing stored glucose from glycogen, rather than by increases in *de novo* synthesis of glucose by gluconeogenesis. Similarly, the reduction in liver glucose output during exercise seen in endurance-trained athletes compared to untrained controls, is primarily driven by a reduction in glycogenolysis, as opposed to changes in gluconeogenesis. Therefore, prolonged exercise of a moderate-to-high intensity leads to a depletion of liver glycogen stores unless carbohydrate is ingested during exercise, particularly in less-trained individuals.

For endurance athletes who require rapid recovery for subsequent competitive events, restoration of skeletal muscle and liver glycogen stores are a primary goal. Carbohydrate ingestion is a requirement to replenish glycogen stores within a 24-h timeframe, and ingesting carbohydrate at a

rate of ~1 g·kg body mass·h^{-1} within the early (0-4 h) recovery period can assist in optimising this process. Whilst muscle glycogen repletion appears to be largely unaffected by the specific presence of fructose in ingested carbohydrates, liver glycogen repletion rates are potently enhanced by the ingestion of fructose- or galactose-containing sugars, when compared to glucose alone. There is evidence that the complete restoration of liver glycogen stores after exhaustive exercise could be accelerated by as much as two-fold with the ingestion of fructose-glucose mixtures, compared to glucose-only carbohydrates. Therefore, athletes with multiple competitive events within a 24-h period should aim to consume ~1 g·kg body mass·h^{-1} of carbohydrate with foods providing fructose and glucose. Not only does this enhance restoration of liver (and therefore total body) glycogen stores, there is now evidence that this can reduce the gut discomfort associated with high-carbohydrate ingestion rates, and improve endurance running capacity. There is, however further work required to establish the optimal dose and mixture of carbohydrates to be ingested to maximise post-exercise liver glycogen recovery.

The rapid restoration of liver glycogen stores is relevant mainly to a small minority of the population engaging in relatively extreme events. Most people are more concerned about their health than competing in an ultra-endurance event. However, the same knowledge gained about the physiological responses to dietary sugars and exercise, particularly hepatic metabolism, can also be applied to improve metabolic health. Fructose containing sugars have been implicated in inducing hyperglycaemia, hypertriglyceridaemia, hepatic insulin resistance and increases in liver fat content, particularly in overweight/obese populations and when in a positive energy balance. Interestingly, there is evidence in young, healthy men that modest amounts of exercise can completely protect against almost all of these potentially deleterious effects of high-fructose intakes, independent of energy balance. The protective effects of exercise may be due to the carbohydrate deficit and/or glycogen turnover in the liver and skeletal muscle induced by physical activity. Accordingly, specifically avoiding carbohydrates at key times: either before, during and/or after exercise to augment and preserve a glycogen deficit, could be a strategy to enhance metabolic health. However, it is not known if exercise can be protective in populations at risk of metabolic disease, which should be a future research priority.

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Conflict of Interest

None.

Authorship

J. T. Gonzalez wrote the initial draft of the manuscript. All authors read, edited and approved of the final manuscript.

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